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(54) Title: MULTIPLE-UNIT TYPE PROLONGED ACTION DRUG PREPARATION

(57) Abstract

The present invention provides a multiple-unit type prolonged release action drug preparation which is characterized by containing at least 2 small tablets of sustained release type drug preparation obtained by formulating cilostazol with hydroxypropylmethylcellulose as the base material of the drug preparation. By formulating cilostazol as in the form of a multiple-unit type prolonged release action drug preparation of the present invention, side-effects, such as headache and other symptoms caused by high blood concentration of cilostazol due to the rapid absorption, can be reduced.

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DESCRIPTION

MULTIPLE-UNIT TYPE PROLONGED ACTION DRUG PREPARATION

TECHNICAL FIELD

The present invention relates to a multiple-unit type prolonged action drug preparation, containing 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyril (non-proprietary name: cilostazol, hereinafter referred to as "cilostazol") as the effective ingredient. More particularly, the invention relates to a multiple-unit type prolonged action drug preparation which comprises at least two small tablets of sustained releasing drug preparation, obtained by formulating cilostazol as the effective ingredient, with a hydroxypropylmethylcellulose as the base material for sustaining release action. Accordingly the pharmacological effect of cilostazol as the effective ingredient can be expressed and sustained for a certain length of time by prolonged releasing of cilostazol, furthermore, the expression of side effects caused by the effective ingredient can be inhibited by controlling rapid absorption of the effective ingredient.

BACKGROUND ART

Cilostazol, which is contained as the effective ingredient in the multiple-unit type prolonged drug preparation of the present invention, has been

described in US-A-4,277,479. Additionally, JP-A-6-239745 discloses that cilostazol can be used as a curing agent for psoriasis, and JP-A-8-73354 discloses that cilostazol is useful for preventing and curing hypersensitivity of the respiratory tract and disturbance of the respiratory tract. Furthermore, WO 93/07217, EP-A-665023 and EP-A-704223 disclose various types of medical materials comprising antithrombotic or antithrombocytic agents like cilostazol.

On the other hand, US-A-4,734,285 discloses solid form medicinal preparations in which hydroxymethylcellulose is used. Additionally, WO 96/21448 discloses preparations for medicinal use which comprises resin particle containing ethylene vinyl alcohol copolymer and cilostazol.

As explained in the above, cilostazol possesses phosphodiesterase inhibitory activity, antiulcerative activity, hypotensive activity, and antiinflammatory activity in addition to the high activity for inhibiting platelet aggregation. Therefore, cilostazol is widely used as agent of antithrombosis, agent for improving circulation of blood flow in the brain, antiinflammatory agent, antiulcerative agent, hypotensive agent, antiasthmatic agent, as well as phosphodiesterase inhibitor.

Cilostazol is generally used as in the form of tablet which is prepared by adding diluents and other ingredients, and the tablet is administered orally.

However, such a tablet containing cilostazol is disintegrated quickly in the stomach, and a large amount of cilostazol is released in the living body in a short time, then the blood concentration of cilostazol is increased, and as a result it may be in danger of bring about side-effects such as headache, heavy head feeling and pains.

SUMMARY OF THE INVENTION

Under in the circumstances, in order to solve these problems occurred in conventional pharmaceutical preparations, the present inventors have made an extensive research work for obtaining a new type of drug preparation containing cilostazol as the effective ingredient, capable to express the pharmacological effects of the effective ingredient for a certain length of time by prolonged releasing of cilostazol in an amount the only necessary to control for increasing the maximum blood concentration of cilostazol, as well as to maintain the blood concentration suitably. As a result, the present invention has been finally completed, thus an object of the present invention can be achieved by formulating cilostazol as in the form of specific multiple-unit type prolonged action drug preparation.

The present invention provides a multiple-unit type prolonged drug preparation which comprises at least two small tablets of sustained release type drug preparation by formulating cilostazol as the effective

ingredient with hydroxypropylmethylcellulose as the drug base material for sustaining release action. By shaping of the drug preparation as in the form of the above-mentioned prolonged action type of tablets, the effective ingredient releasing from each one of these small tablets can be controlled for a certain length of time, while the blood concentration of the effective ingredient can be maintained in the necessary level by administering the small tablets in plural number at the same time.

As can be seen from the data shown in experiments disclosed later on, the multiple-unit type prolonged drug preparations of the present invention have the feature of capability to keep the blood concentration of the effective ingredient stably for a certain length of time, because when the drug preparation is administered, then the effective ingredient can be absorbed in constant level without affected due to physiological conditions of the living body being administered.

DISCLOSURE OF THE INVENTION

The multiple-unit type prolonged drug preparation of the present invention is prepared by formulating cilostazol as the effective ingredient with hydroxypropylmethylcellulose (hereinafter referred to as "HPMC") as the base material for sustaining release drug preparation, and if desired said drug preparation may be

further formulated with other conventional type diluents by usual method to prepare and shaped into a form of small tablet of drug preparation, then at least two small tablets of sustained release type drug preparation are packed in a capsule or shaped into other administration unit forms.

As to an HPMC used for the base material of the sustaining release drug preparation, any commercially available HPMC can be used, particularly an HPMC of which aqueous solution gives high viscosity may preferably be used. For example, an HPMC, of which aqueous solution in concentration of 2% by weight gives the viscosity higher than 400 cps at 20°C, is preferable, particularly an HPMC of which aqueous solution gives the viscosity higher than 400 to 200,000 cps may be used preferably. The ratio of amount of HPMC to be formulated in the drug preparation is 10 to 90% by weight, preferably 30 to 80% by weight to the whole amount of the small tablet of sustained release type drug preparation.

Said small tablet of sustained release type drug preparation is prepared by formulating a prescribed amount of cilostazol as the effective ingredient with a suitable amount of HPMC, and if desired pharmaceutically acceptable common diluent may be added thereto, then the whole mixture is shaped into the form of small tablet by a usual method, for example wet-granulation or dry-granualtion.

As to the base material for the sustaining release drug preparation, those of known in this technical field can be widely used, for example, diluents such as lactose, white sugar, sodium chloride, glucose, starch, calcium carbonate, kaolin, crystalline cellulose, silicates and the like; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxy-methylcellulose-Na, shelac, methylcellulose, hydroxy-propylcellulose, polyvinyl alcohol and the like; disintegraters such as dried starch, agar-agar powder, calcium carboxymethylcellulose, sodium hydrogen-carbonate, calcium carbonate, fatty acid esters of polyoxyethylenesorbitan, sodium laurylsulfate, mono-glyceride of stearic acid, starch and the like; absorption promotors such as quaternary ammonium bases and the like; lubricants such as refined talc, stearates, boric acid powder, polyethylene glycols, colloidal silicic acid and the like; plasticizers such as fatty acid esters of glycerin, dioctyl phthalate, dibutyl phthalate, triacetin, castor oil and the like can be exemplified. These pharmaceutically acceptable diluents can be suitably selected and used.

Thus prepared small tablet of sustained release type drug preparation may have generally a size of 3 to 7 mm in diameter, preferably 4 to 6 mm, more preferably 5 to 6 mm in diameter, and may have generally a weight of 10 to 300 mg, preferably 20 to 120 mg, more

preferably 40 to 80 mg per one small tablet. At least 2, preferably 2 to 20, more preferably 3 to 10, yet further preferably 4 to 7 of these small tablets are packed into a form of multiple-unit type prolonged drug preparation. Said multiple-unit type prolonged drug preparation may be shaped in any type of administration form provided that, 2 or more of the small tablets of sustained release type drug preparation are involved into one administration unit form. Generally, a capsule form preparation in which the prescribed number of small tablets of sustained release type drug preparation are packed in one capsule, or a heat-sealed pack form preparation in which the prescribed number of small tablets of sustained release type drug preparation are sealed into one heat-sealed pack may be used preferably.

Dose of cilostazol as the active ingredient to be contained in the multiple-unit type prolonged drug preparation of the present invention is varied depend on age of the patient, distinguish of sex, body weight as well as symptom of the patient, generally cilostazol may be administered in an amount of 1 to 500 mg per day, preferably 50 to 200 mg, more preferably 100 to 200 mg per day. In the multiple-unit type prolonged drug preparation of the present invention, cilostazol is formulated to give in an amount of the above-mentioned dose per day. For example, for obtaining a multiple-unit type prolonged drug preparation containing 100 mg of cilostazol as the dose per day, small tablets of

sustained release type drug preparation containing 10 mg each of cilostazol are prepared at first, then 10 of these small tablets are packed into a capsule; or 5 of these small tablets are packed into 2 capsules, and these 2 capsules are orally administered at the same time a day, or each one of these capsules in which 5 of these small tablets are packed in one capsule are orally administered separately twice a day. On the other hand, small tablets of sustained release type drug preparation containing 50 mg each of cilostazol are prepared, then 2 of these small tablets are packed into a capsule to make a capsule preparation containing 100 mg of cilostazol as to the dose per day. As there is explained in the above, the multiple-unit type prolonged drug preparation of the present invention has advantageous points in that the dose of cilostazol per day, as well as the amount of cilostazol to be contained in an administration unit can be controlled freely by adjusting suitably the formulation amount of cilostazol as the effective ingredient.

The multiple-unit type prolonged drug preparation of the present invention may only contains plural number of the above-mentioned small tablets of sustained release type drug preparation, or may be prepared by formulating at least 2 of the small tablets of sustained release type drug preparation together with other small tablets (hereinafter referred to as "small tablets of rapid release type drug preparation") which is prepared by formulating cilostazol as the effective ingredient

with common pharmaceutically acceptable diluents, but without using HPMC as a drug base material for sustaining release. Said small tablets of rapid release type drug preparation may be formulated with the amount of less than 60%, preferably 10 to 60%, more preferably 10 to 40% to the whole amount of the objective multiple-unit type prolonged drug preparation. For example, a capsule form multiple-unit type prolonged drug preparation which contains 100 mg of cilostazol can be obtained by packing 5 small tablets of sustained release type drug preparation containing 10 mg of cilostazol, together with 5 small tablets of rapid release type drug preparation containing 10 mg of cilostazol into one capsule. As a matter of course, the formulation amount of cilostazol to be contained in each one of the small tablets of sustained release type drug preparation and in the small tablets of rapid release type drug preparation can be changed freely. The releasing characteristics of cilostazol and its blood concentration can be freely controllable by suitable combination of the small tablets of sustained release type drug preparation and the small tablets of rapid release type drug preparation.

The releasing characteristics of cilostazol to be contained in the multiple-unit type prolonged drug preparation of the present invention can be controllable, in that, by prolonged releasing of cilostazol and regulating rapid increase of the blood concentration of

cilostazol, so that undesirable side-effects such as headache and heavy head feeling can be prevented. Also, the drug preparation of the present invention possesses advantage for reducing the time of administrations according to prolonged releasing of cilostazol. The multiple-unit type prolonged drug preparation of the present invention possesses the advantageous point in that constant level of cilostazol can be absorbed continuously when it is administered to a patient in the cases of hunger and after a meal, there is not any big difference in velocity of releasing cilostazol between these two cases, also the absorption of cilostazol into the living body is not affected depend on the changes in physiological conditions of the patient, also is not almost affected by the individual difference of the patients at all.

WORKING EXAMPLES OF THE INVENTION

Next, the multiple-unit type prolonged drug preparations of the present invention and their pharmacological effect will be explained more concretely by illustrating Examples, Comparative tests and Experiments as follows.

Example 1

Small tablets of sustained release type drug preparation were prepared according to the formulations as follows.

Ingredients	Formulation amount
Cilostazol	1,000 g
HPMC 2910 (Manufacture by Shin-Etsu Chemical Co., Ltd.; Metolose 60SH4000; viscosity of 2% solution at 20°C: 4,000 cps)	1,940 g
Hydroxypropylcellulose (Manufactured by Nippon Soda Co., Ltd. HPC-L)	30 g
Magnesium stearate	30 g

1,000 Grams of cilostazol and 1,940 g of HPMC were mixed together, and to this mixture was added 30 g of an aqueous solution of hydroxypropylcellulose as a binder, the whole mixture was subjected to a wet-granulation by use of a kneading-granulator (model: Vertical Granulator VG-25, manufactures by PowRex & Co.). Thus obtained granulated products were dried, and classified by screening, then 30 g of magnesium stearate as a lubricant was added thereto and mixed to obtain as tableting powder. This tableting powder was subjected to tableting process by a continuous tableting machine (model 812 HUK, manufactured by Kikusui Seisakusho Co.) by use of a die and punches having 5 mm in diameter to prepare tablets having 60 mg of weight per one tablet (containing 20 mg of cilostazol).

Five small tablets of sustained release type drug preparation thus obtained were packed into a capsule to make a multiple-unit type prolonged drug preparation (containing 100 mg of cilostazol per one capsule).

Examples 2 to 3 and Comparative examples 1 to 6

As can be seen from the following Table 1, by procedure similar to that employed in Example 1, small tablets of sustained release type drug preparation were prepared (the weight of small tables obtained in Examples 2 to 3 and Comparative examples 1, 3 and 5 were 50 mg each; and those of obtained in Comparative examples 2, 4 and 6 were 60 mg each; the contents of cilostazol in these small tablets were 20 mg each), then 5 tablets each of the small tablets were packed in one capsule so as to make multiple-unit type prolonged drug preparations.

Table 1

(Formulation unit: g)

Ingredients	Example 2	Example 3	Comparative example 1	Comparative example 2
Cilostazol	100.0	100.0	100.0	100.0
HPMC 2910 (*1)	75.0	125.0	-	-
MC (*2)	-	-	75.0	194.0
Sodium alginate (*3)	-	-	-	-
HPC-H (*4)	-	-	-	-
Lactose	70.0	20.0	70.0	-
HPC-L (*5)	2.5	2.5	2.5	3.0
Mg-St (*6)	2.5	2.5	2.5	3.0
Total	250.0	250.0	250.0	300.0

(*1) Hydroxypropylmethylcellulose [Viscosity: 4,000 cps, 2%, at 20°C, (Tradename: Metolose 60SH4000, manufactured by Shin-Etsu Chemical Co., Ltd.)]

(*2) Methylcellulose [Viscosity: 4,000 cps, 2%, at 20°C, (Tradename: Metolose 60SM4000, manufactured by Shin-Etsu Chemical Co., Ltd.)]

(*3) Sodium alginate [Viscosity: 500~600 cps, 1%, at 20°C, (manufactured by Wako Pure Chemical Industries, Co., Ltd.)]

(*4) Hydroxypropylcellulose [Viscosity: 1,000~4,000 cps, 2%, at 20°C, (Tradename: HPC-H, manufactured by Nippon Soda Co., Ltd.)]

(*5) Hydroxypropylcellulose (Tradename: HPC-L, manufactured by Nippon Soda Co., Ltd.)

(*6) Magnesium stearate

Table 1 (Continued)

(Formulation unit: g)

Ingredients	Comparative example 3	Comparative example 4	Comparative example 5	Comparative example 6
Cilostazol	100.0	100.0	100.0	100.0
HPMC 2910 (*1)	-	-	-	-
MC (*2)	-	-	-	-
Sodium alginate (*3)	75.0	194.0	-	-
HPC-H (*4)	-	-	75.0	194.0
Lactose	70.0	-	70.0	-
HPC-L (*5)	2.5	3.0	2.5	3.0
Mg-St (*6)	2.5	3.0	2.5	3.0
Total	250.0	300.0	250.0	300.0

(*1) to (*6) are the same as defined previously.

Comparative examples 7 and 8

In accordance with the following formulations shown in Table 2, tablets of sustained release drug preparation were obtained similarly by the procedures those employed in Example 1, provided that the weight of each one of the tablets was made to 170 mg (content of cilostazol: 100 mg each). Each of the tablets was made as to a single-unit administration form for the single-unit type prolonged drug preparation.

Table 2

(Formulation unit: g)

Ingredients	Comparative example 7	Comparative example 8
Cilostazol	100.0	100.0
HPMC 2910 (*1)	20.0	40.0
Lactose	46.0	26.0
Hydroxypropylcellulose	2.0	2.0
Magnesium stearate	2.0	2.0
Total	170.0	170.0

(*1) is the same as defined previously.

Examples 4 to 24

In accordance with the following formulations shown in Table 3, small tablets of sustained release type drug preparation were obtained similarly by the procedures those employed in Example 1 (unit of each one of the ingredients to be formulated: g). The weight of each one of the small tablets, the content of cilostazol and the number of small tablets to be packed in the multiple-unit type prolonged drug preparation (one capsule) of the present invention are indicated in Table 3.

Table 3

(Formulation unit: g)

Ingredients	Example 4	Example 5	Example 6
Cilostazol	100.0	100.0	100.0
HPMC 2910 (*1)	45.0	395.0	395.0
Lactose	3.5	-	-
Magnesium stearate	1.5	5.0	5.0
Total	150.0	500.0	500.0
Weight of a small tablet (Content of cilostazol)	50 mg (33.3 mg)	50 mg (10 mg)	100 mg (20 mg)
Number of small tablets packed in a capsule	3	10	5

(*1) is the same as defined previously.

Table 3 (Continued)

(Formulation unit: g)

Ingredients	Example 7	Example 8	Example 9
Cilostazol	100.0	100.0	100.0
HPMC 2910 (*1)	12.0	12.0	12.0
Lactose	6.8	6.8	6.8
Magnesium stearate	1.2	1.2	1.2
Total	120.0	120.0	120.0
Weight of a small tablet (Content of cilostazol)	60 mg (50 mg)	40 mg (33.3 mg)	20 mg (16.7 mg)
Number of small tablets packed in a capsule	2	3	6

(*1) is the same as defined previously.

Table 3 (Continued)

(Formulation unit: g)

Ingredients	Example 10	Example 11	Example 12
Cilostazol	100.0	100.0	100.0
HPMC 2910 (*1)	72.0	480.0	480.0
Lactose	6.2	14.0	14.0
Magnesium stearate	1.8	6.0	6.0
Total	180.0	600.0	600.0
Weight of a small tablet (Content of cilostazol)	60 mg (33.3 mg)	60 mg (10 mg)	120 mg (20 mg)
Number of small tablets packed in a capsule	3	10	5

(*1) is the same as defined previously.

Table 3 (Continued)

(Formulation unit: g)

Ingredients	Example 13	Example 14	Example 15
Cilostazol	100.0	50.0	50.0
HPMC 2910 (*1)	1080.0	97.0	100.0
Lactose	8.0	1.5	840.0
Magnesium stearate	12.0	1.5	10.0
Total	1200.0	150.0	1000.0
Weight of a small tablet (Content of cilostazol)	60 mg (5 mg)	50 mg (16.7 mg)	50 mg (2.5 mg)
Number of small tablets packed in a heat-sealed pack	20	3	20

(*1) is the same as defined previously.

Table 3 (Continued)

(Formulation unit: g)

Ingredients	Example 16	Example 17	Example 18
Cilostazol	50.0	50.0	50.0
HPMC 2910 (*1)	10.0	10.0	10.0
Lactose	39.0	39.0	39.0
Magnesium stearate	1.0	1.0	1.0
Total	100.0	100.0	100.0
Weight of a small tablet (Content of cilostazol)	50 mg (25 mg)	25 mg (12.5 mg)	20 mg (10 mg)
Number of small tablets packed in a capsule	2	4	5

(*1) is the same as defined previously.

Table 3 (Continued)

(Formulation unit: g)

Ingredients	Example 19	Example 20	Example 21
Cilostazol	50.0	50.0	50.0
HPMC 2910 (*1)	66.0	66.0	66.0
Lactose	2.8	2.8	2.8
Magnesium stearate	1.2	1.2	1.2
Total	120.0	120.0	120.0
Weight of a small tablet (Content of cilostazol)	60 mg (25 mg)	40 mg (16.7 mg)	20 mg (8.3 mg)
Number of small tablets packed in a capsule	2	3	6

(*1) is the same as defined previously.

Table 3 (Continued)

(Formulation unit: g)

Ingredients	Example 22	Example 23	Example 24
Cilostazol	50.0	50.0	50.0
HPMC 2910 (*1)	126.0	540.0	540.0
Lactose	2.2	4.0	4.0
Magnesium stearate	1.8	6.0	6.0
Total	180.0	600.0	600.0
Weight of a small tablet (Content of cilostazol)	60 mg (16.7 mg)	60 mg (5 mg)	120 mg (10 mg)
Number of small tablets packed in a capsule	3	10	5

(*1) is the same as defined previously.

Example 25

(1) Preparation of small tablets of rapid release type drug preparation

1,000 Grams of cilostazol, 750 g of corn starch (manufactured by Nihon Shokuhin Kako Co., Ltd.) and 500 g of crystalline cellulose (manufactured by Asahi Chemical Industry Co., Ltd.) were mixed together, then to this mixture was added an aqueous solution of 25 g of hydroxypropylcellulose (HPC-L, manufactured by Nippon Soda Co., Ltd.) as a binder, then the whole mixture was subjected to wet-granulation by use of a kneading-granulating machine (model: Vertical Granulator VG-25, manufactured by PowRex & Co.). Thus obtained granulated products were dried, and classified by

screening, then 200 g of carmellose calcium (tradename: ECG 505, manufactured by Nichirin Kagaku Co., Ltd.) as a disintegrator, and 25 g of magnesium stearate (manufactured by Taihei Kagaku Sangyo Co., Ltd.) as a lubricant were added thereto, and mixed to obtain as tableting powder. This powder was subjected to tableting process by use of a continuous tableting machine (model: 812HUK, manufactured by Kikusui Seisakusho Co.) by use of a die and punches having a size of 5 mm in diameter to prepare tablets having 50 mg of weight per one tablet (containing 20 mg of cilostazol) to obtain small tablets of rapid releasing type drug preparation.

(2) Preparation of multiple-unit type prolonged release drug preparation

Multiple-unit type prolonged release drug preparation (containing 100 mg of cilostazol per one capsule) was prepared by packing 3 small tablets of sustained release type drug preparation obtained in Example 1 in one capsule, also 2 small tablets of rapid release type drug preparation obtained previously were also packed in the same capsule.

Example 26

Multiple-unit type prolonged release drug preparations were prepared by procedure similar to that of employed in Example 1, except that die and punches having different diameters (3 mm, 4 mm, 5.2 mm, 5.5 mm, 6 mm and 7 mm), were used, respectively.

Experiment 1 (Dissolution tests)

Drug preparations of Examples 1 and 2, as well as Comparative examples 1 to 6 were used for dissolution tests by the paddle method and paddle-beads method.

(1) Paddle method

This method was provided as a model for administration of a drug preparation in fasting condition.

As to the test liquid, an aqueous solution of 0.3% sodium laurylsulfate was used. A drug preparation to be tested was added into this test liquid. The test was conducted by procedures in accordance with the second paddle method as prescribed in Japanese Pharmacopoeia (13th Revised Ed.) by rotating the paddle at 75 rpm. The dissolved amount of cilostazol was measured continuously by use of a flow cell, and the time (P) for requiring to dissolve 75% of the whole amount of cilostazol was determined.

(2) Paddle-beads method

This method was provided as a model for administration of a drug preparation in non-fasting condition by adding mechanical destructive force to the drug preparation.

As to the test liquid, an aqueous solution of 0.3% sodium laurylsufate was used. This test liquid together with the drug preparation to be tested were put in a vessel of dissolution test. Additionally, 2,000 pieces of beads made of plastic having about 6 mm in diameter were also put into the vessel. The test was

conducted by procedures in accordance with the second paddle method as prescribed in Japanese Pharmacopoeia (13th Revised Ed.) by rotating the paddle at 50 rpm. The dissolved amount of cilostazol was measured continuously by use of a flow cell, and the time (PB) for requiring to dissolve 75% of the whole amount of cilostazol was determined.

The test results are shown in Table 4.

Table 4

(Unit: minute)

	Test samples of drug preparation			
	Example 1	Example 2	Comparative example 1	Comparative example 2
Paddle method (P)	282	177	28	44
Paddle-beads method (PB)	228	145	15	27
PB/P	0.81	0.82	0.54	0.61

Table 4 (Continued)

(Unit: minute)

	Test samples of drug preparation			
	Comparative example 3	Comparative example 4	Comparative example 5	Comparative example 6
Paddle method (P)	89	101	623	874
Paddle-beads method (PB)	34	42	259	427
PB/P	0.38	0.42	0.42	0.49

As can be seen from the test results shown in Table 4, in comparison with the dissolution velocities (times for requiring to dissolve 75% of the whole amount of cilostazol), there are not any big significant difference in the dissolution times between the model for administration of a multiple-unit type prolonged release action drug preparation in fasting condition measured by the paddle method, and in non-fasting condition measured by the paddle-beads method. Thus excellent prolonged releasing characteristics of the multiple-unit type prolonged release action drug preparations of the present invention were performed without bring any big difference of the pharmacokinetics due to the changes in physiological conditions of the test subjects.

On the contrary, the drug preparations of Comparative examples 1 to 6 which were obtained by without using the base material for the drug preparation of the present invention, there are quite big difference of the pharmacokinetics between the administrations in fasting condition and in non-fasting condition. While, in comparing with drug preparations obtained by using methylcellulose (Comparative examples 1 and 2) and sodium alginate (Comparative examples 3 and 4) as to the base materials for sustaining release action, the velocities for dissolving cilostazol performed by these drug preparations were quite rapidly, thus releasing of cilostazol could not be controlled at all.

Experiment 2 (Pharmacokinetics in case of administration in non-fasting condition)

In order to investigate the pharmacokinetics in case of administering the test drug preparation in non-fasting condition, each samples of test drug preparations (each contains 100 mg of cilostazol) as indicated in the following Table 5 was orally administered once to volunteers after the breakfast. After the administration, samples of the blood were taken from the volunteer time sequently, and the blood concentrations of cilostazol were measured and investigated the maximum observed plasma concentration (C_{max}), the time of C_{max} (T_{max}) and the area under the plasma concentration-time curve (AUC_{0-72hr}).

As to the reference test, one tablet of "Pletaal 100" (tradename for cilostazol tablet containing 100 mg thereof, manufactured by Otsuka Pharmaceutical Co., Ltd.) was orally administered similarly to volunteers, and C_{max}, T_{max} and AUC_{0-72hr} determined from the reference test were defined as to the value of 100%, and the percentage (%) of C_{max}, T_{max} and AUC_{0-72hr} determined from each of test samples were calculated.

The results are shown in Table 5.

Table 5

Drug preparation for testing (n: Number of subjects)	Parameters of pharmacokinetics (Mean value ± SE)		
	C_{max} (ng/ml)	AUC_{0-72hr} (ng·hr/ml)	T_{max} (Hour)
Pletaal (n=6)	1833 ± 167 (100%)	13776 ± 2042 (100%)	4.3 ± 0.5 (100%)
Example 1 (n=11)	1160 ± 142 (62%)	13798 ± 1341 (100%)	7.4 ± 0.4 (172%)
Example 2 (n=6)	1259 ± 114 (67%)	11782 ± 1568 (86%)	6.3 ± 0.4 (147%)
Example 3 (n=12)	1198 ± 128 (64%)	11345 ± 840 (82%)	6.7 ± 0.4 (156%)
Comparative example 7 (n=6)	1086 ± 135 (58%)	9693 ± 1392 (70%)	5.0 ± 0.5 (116%)
Comparative example 8 (n=6)	918 ± 93 (49%)	8864 ± 1331 (64%)	5.2 ± 0.3 (121%)

As can be seen from the test results shown in Table 5, any one of the multiple-unit type prolonged release action drug preparations (Examples 1, 2 and 3) of the present invention show sufficient value of the area under the plasma concentration-time curve (AUC), while they inhibit the maximum observed plasma concentration (C_{max}) as compared with that of shown by "Pletaal" tablet (commercially available product), thus

the side-effects such as headache and the like which are caused by high blood concentration could be controlled.

On the contrary, single-unit type drug preparations (Comparative examples 7 and 8) can be controlled the maximum observed plasma concentration (C_{max}), but they have drawbacks in that sufficient value of the area under the plasma concentration-time curve (AUC) could not have been obtained, for the reason that dissolution of cilostazol could be controlled at the same time.

Furthermore, the multiple-unit type prolonged release action drug preparations perform considerable prolongation of the time of C_{max} (T_{max}) as compared with that of shown by "Pletaal" tablet (commercially available product). On the contrary, by the single-unit type drug preparations, sufficient prolongation of the time of C_{max} (T_{max}) were not observed.

CLAIMS

1. A multiple-unit type prolonged action drug preparation characterized by containing at least 2 small tablets of sustaining release action type drug which comprises 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyril as the effective ingredient, and formulated therewith hydroxypropylmethylcellulose as a drug base material for sustaining release action.

2. The multiple-unit type prolonged action drug preparation according to Claim 1, wherein the hydroxypropylmethylcellulose gives a viscosity of higher than 400 cps, and said hydroxypropylmethylcellulose is formulated in the ratio of 10 to 90 % by weight to the whole amount of the small tablet of sustained release action type drug.

3. The multiple-unit type prolonged action drug preparation according to Claim 2, which contains 2 to 20 of the small tablets of sustained release action type drug having the size of 3 to 7 mm in diameter and the weight of each one of the small tablet is 10 to 300 mg.

4. The multiple-unit type prolonged action drug preparation according to Claim 3, wherein the hydroxypropylmethylcellulose gives a viscosity of 400 to 200,000 cps.

5. The multiple-unit type prolonged action drug preparation according to Claim 4, wherein the weight of each one of the small tablet of sustained release action type drug is 20 to 120 mg.

6. The multiple-unit type prolonged action drug preparation according to Claim 5, which contains 3 to 10 of the small tablets of sustained release action type drug having the size of 4 to 6 mm in diameter.

7. The multiple-unit type prolonged action drug preparation according to Claim 6, wherein the hydroxypropylmethylcellulose is formulated in the ratio of 30 to 80 % by weight to the whole amount of the small tablets of sustained release action type drug.

8. The multiple-unit type prolonged action drug preparation according to Claim 7, which contains 4 to 7 of the small tablets of sustained release action type drug.

9. The multiple-unit type prolonged action drug preparation according to Claim 8, wherein the size of the small tablet of sustained release action type drug is 5 to 6 mm in diameter, and the weight of each one of said small tablet is 40 to 80 mg.

10. The multiple-unit type prolonged action drug preparation according to Claim 7, wherein the weight of each one of the small tablet of sustained release action type drug is 40 to 80 mg.

11. The multiple-unit type prolonged action drug preparation according to Claim 10, which contains 4 to 7 of the small tablets of sustained release action type drug.

12. The multiple-unit type prolonged action drug preparation according to Claim 7, wherein the size of

the small tablets of sustained release action type drug is 5 to 6 mm in diameter.

13. The multiple-unit type prolonged action drug preparation according to Claim 5, wherein the hydroxypropylmethylcelulose is formulated in the ratio of 30 to 80 % by weight to the whole amount of the small tablets of sustained release action type drug.

14. The multiple-unit type prolonged action drug preparation according to Claim 13, wherein the size of the small tablet of sustained release action type drug is 4 to 6 mm in diameter, and the weight of each one of said small tablet is 40 to 80 mg.

15. The multiple-unit type prolonged action drug preparation according to Claim 13, which contains 4 to 7 of the small tablets of sustained release action type drug.

16. The multiple-unit type prolonged action drug preparation according to Claim 1, in addition to at least 2 of the small tablets of sustained release type drug preparation, which further contains 1 or at least 2 of small tablets of rapid release type drug preparation containing 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)-butoxy]-3,4-dihydrocarbostyril as the effective ingredient.

17. The multiple-unit type prolonged action drug preparation according to Claim 16, in addition to 2 to 20 of the small tablets of sustained release type drug preparation, which is further formulated with less than 60% of the small tablets of rapid release type drug

preparation to the whole amount of the multiple-unit type prolonged action drug preparation.

18. The multiple-unit type prolonged action drug preparation according to Claim 17, in addition to 3 to 10 of the small tablets of sustained release type drug preparation, which is further formulated with 10 to 60% of the small tablets of rapid release type drug preparation to the whole amount of the multiple-unit type prolonged action drug preparation.

19. The multiple-unit type prolonged action drug preparation according to Claim 18, which is formulated with 10 to 40% of the small tablets of rapid release type drug preparation to the whole amount of the multiple-unit type prolonged action drug preparation.

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(57) Abstract

The present invention provides a multiple-unit type prolonged release action drug preparation which is characterized by containing at least 2 small tablets of sustained release type drug preparation obtained by formulating cilostazol with hydroxypropylmethylcellulose as the base material of the drug preparation. By formulating cilostazol as in the form of a multiple-unit type prolonged release action drug preparation of the present invention, side-effects, such as headache and other symptoms caused by high blood concentration of cilostazol due to the rapid absorption, can be reduced.

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